I Systems Microbiology (13 Lectures)

'The cell as a well-stirred biochemical reactor'

L1	Introduction
L2	Chemical kinetics, Equilibrium binding, cooperativity
L3	Lambda phage
L4	Stability analysis
L5-6	Genetic switches
L7-9	*E. coli* chemotaxis
L10-11	Genetic oscillators
L12-13	Stochastic chemical kinetics

II Systems Cell Biology (9 Lectures)

‘The cell as a compartmentalized system with concentration gradients’

L15 Diffusion, Fick’s equations, boundary and initial conditions
L16-17 Local excitation, global inhibition theory
L18-19 Models for eukaryotic gradient sensing
L20-21 Center finding algorithms
L22-23 Modeling cytoskeleton dynamics

III Systems Developmental Biology (2 Lectures)

'The cell in a social context communicating with neighboring cells'

L23 Quorum sensing
L25 Drosophila development

Main take home messages from this course:

1. translate the biology into a quantitative model:

given the biology set up the coupled differential equations that capture the essence of the biological phenomena

(not trivial since 4 papers came up with a different model given the same biological phenomenon, which assumptions to make is critical)

2. analysis of the system of differential equations

stability analysis (both in space and time)

3. interpretation of the mathematical analysis, what are the biological conclusions ?

e.g. if the imaginary part of the eigenvalue is non zero, what does this mean for the underlying biology?

4. develop a taste for the potential of these systems approaches for biological problems that you may encounter in the future

Developmental Systems Biology

'Building an organism
starting from a single cell'

Introducing: *Drosophila melanogaster*
(or the fruitfly)

Great book: 'The making of the fly' by
Peter Lawrence

major advantage of Drosphila:

each stripe in the embryo corresponds to certain body parts in adult fly

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MOVIE !

http://flymove.uni-muenster.de

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Pioneering experiments by Klaus Sander (1958) on leaf-hoppers

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ligation and transplantation experiments indicate the presence of morphogens created/destroyed at the poles of the embryo

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First morphogen:
bicoid (true maternal)

transplantation of bicoid
can rescue cells

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head fold shift to
right for increasing
number of gene copies
in mother

interpreting the bicoid gradient (created by maternal effects) by zygotic effect (gene expression by embryo itself)

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hunchback reads
the bicoid gradient

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recent experimental paper explores relation between bicoid and hunchback quantitatively:

Houchmandzadeh et al. Nature 415, 798 (2002).

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How can you make a steep step in hunchback exactly in the middle of the embryo from a noisy bicoid gradient ?

Nobody knows ...

Second example:

Robustness of Drosophila patterning
Eldar et al., Nature **419**, 304 (2002)

remember robustness of chemotaxis (L9-10):

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explore robustness in Drosophila patterning

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main molecules of interest:

Scw: BMP (bone morphogenic protein) ligand

Sog: a BMP inhibitor

Tld: protease (cleaves Sog)

simple reaction-diffusion model:

$$\frac{\partial [Sog]}{\partial t} = D_S \frac{\partial^2 [Sog]}{\partial x^2} - k_b [Sog][Scw] + k_{-b}[Sog-Scw] - \alpha [Tld][Sog]$$

$$\frac{\partial [Scw]}{\partial t} = D_{BMP} \frac{\partial^2 [Scw]}{\partial x^2} - k_b [Sog][Scw] + k_{-b}[Sog-Scw] + \lambda [Tld][Sog-Scw]$$

$$\frac{\partial [Sog-Scw]}{\partial t} = D_C \frac{\partial^2 [Sog-Scw]}{\partial x^2} + k_b [Sog][Scw] - k_{-b}[Sog-Scw] - \lambda [Tld][Sog-Scw]$$

what does this mean ?

robustness analysis

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$$\frac{\partial[Sog]}{\partial t} = D_S \frac{\partial^2[Sog]}{\partial x^2} - k_b[Sog][Scw] + k_{-b}[Sog-Scw] - \alpha[Tld][Sog]$$

$$\frac{\partial[Scw]}{\partial t} = D_{BMP} \frac{\partial^2[Scw]}{\partial x^2} - k_b[Sog][Scw] + k_{-b}[Sog-Scw] + \lambda[Tld][Sog-Scw]$$

$$\frac{\partial[Sog-Scw]}{\partial t} = D_C \frac{\partial^2[Sog-Scw]}{\partial x^2} + k_b[Sog][Scw] - k_{-b}[Sog-Scw] - \lambda[Tld][Sog-Scw]$$

why robust, ideal model: $D_{BMP}=0$, $\alpha=0$, $k_{-b}=0$

$$0 = D_S \frac{\partial^2[Sog]}{\partial x^2} - k_b[Sog][Scw]$$

$$0 = 0 - k_b[Sog][Scw] + \lambda[Tld][Sog-Scw] \longrightarrow \frac{\partial^2}{\partial x^2}\frac{1}{[Scw]} = \frac{k_b}{D_S}$$

$$0 = D_C \frac{\partial^2[Sog-Scw]}{\partial x^2} + k_b[Sog][Scw] - \lambda[Tld][Sog-Scw]$$